

**REMARKS**

Claims 21-45 are pending in the application. Claims 21, 22, and 32-45 are withdrawn as being drawn to non-elected inventions. Claims 23-31 are under active consideration. Claims 23 and 28 have been amended such that they no longer depend on non-elected claims in order to address the rejection under 35 U.S.C. § 112, second paragraph. Claim 25 has been amended such that it does not depend on a canceled claim.

As amended, claim 23 reads as follows:

An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

- a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2,
- b) a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1, said polypeptide having antigen binding activity
- c) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2, said polypeptide having GTPase effector activity,
- d) an immunogenic fragment consisting of at least 20 contiguous amino acid residues of an amino acid sequence of SEQ ID NO:2,
- e) a biologically active fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:1, said fragment having antigen binding activity, and
- f) a biologically active fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, said fragment having GTPase effector activity.

Support for the amendment to claim 23 b) and e) can be found in the specification, for example, at page 13, lines 25-34, which point out regions of homology between SEQ ID NO:1 and the immunoglobulin κ light chain, and at page 47, line 14 through page 48, line 1 and at page 49, line 29 through page 50, line 6, which describe assays for measuring antigen binding activity.

Support for the amendment to claim 23 c) and f) can be found in the specification, for example, at page 14, lines 14-24 and in Figure 3, which points out regions of homology between SEQ ID NO:2 and MSE55. In addition, a recent Blast analysis shows that SEQ ID NO:2 is 100% identical to human Borg2 (g5731207). See the BLAST analysis attached at Exhibit A and the enclosed article of Joberty et al. (1999) Mol. Cell. Biol. 19:6585-6597 describing the members of the Borg family of GTPase effector proteins, which include MSE55 (also known as Borg5) and Borg2. Entry of these amendments is respectfully requested. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

**Comments Regarding Restriction Requirement**

Applicants affirm the election with traverse of Group II, which corresponds to claims 23-31 drawn to polynucleotides.

As currently amended, the claims drawn to polypeptides and the claims drawn to polynucleotides are free of prior art. (See the discussion below regarding the rejection under 35 U.S.C. § 102(a).) Therefore, the objection of lack of unity based on prior art should be withdrawn. Applicants reiterate the request that the Examiner withdraw the Restriction Requirement at least with respect to claims 21, 22, 35, and 36 of Group I, and examine those claims together with the elected polynucleotide claims of Group II.

The rules under MPEP section 1893.03(d) require the Examiner to apply the Unity of Invention standard PCT Rule 13.2 instead of U.S. restriction/election of species practice in national stage applications, such as the instant application filed under 35 U.S.C. 371. Applicants submit that claims drawn to the polypeptide sequences of SEQ ID NO:1 and SEQ ID NO:2 (*i.e.*, claims 21, 22, 35, and 36) and claims drawn to the elected polynucleotide sequences of SEQ ID NO:3 and SEQ ID NO:4, which encode SEQ ID NO:1 and SEQ ID NO:2, respectively (*i.e.*, claims 23-31) meet the unity of invention standards based on the rules concerning unity of invention under the Patent Cooperation Treaty.

The Administrative Instructions Under The Patent Cooperation Treaty, Annex B, Unity of Invention, Part 2, "Examples Concerning Unity of Invention" provide the following guidelines with regard to unity of invention between a protein and the polynucleotide that encodes it:

*Example 17*

Claim 1: Protein X.

Claim 2: DNA sequence encoding protein X.

Expression of the DNA sequence in a host results in the production of a protein which is determined by the DNA sequence. The protein and the DNA sequence exhibit corresponding special technical features. Unity between claims 1 and 2 is accepted.

Applicants submit that Example 17 does apply to the claims of the instant application, since the polynucleotides of SEQ ID NO:3 and SEQ ID NO:4 encode the polypeptides of SEQ ID NO:1 and SEQ ID NO:2, respectively. In particular, claims 21 and 23 meet the unity of invention standards. Unity of invention is accepted between a protein and the polynucleotide that encodes it. Refusal to examine claims drawn to the polynucleotides and polypeptides

together on the grounds that the polynucleotides are structurally distinct from the polypeptides is improper.

### **Rejoinder of method claims upon allowance of product claims under U.S. practice**

The Examiner is reminded that claims 32-34, 39, and 40, drawn to methods of using the elected polynucleotides of Group II should be rejoined per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of any product claim, for rejoinder of process claims covering the same scope of products. Applicants request that claims 32-34, 39, and 40 be rejoined and examined upon allowance of any claim drawn to the polynucleotides of Group II.

### **Objection to the Specification**

The priority information has been revised as suggested by the Examiner to include a reference to the National Stage International Application No. PCT/US99/22908 filed under 35 U.S.C. § 371. Withdrawal of the objection to the specification is therefore requested.

### **Utility Rejections under 35 U.S.C. §101 and §112, First Paragraph**

Claims 23-31 are rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The Office Action alleges in particular that "the claimed invention lacks a credible, substantial, specific, or well established utility" (Office Action, page 3). Applicants respectfully traverse the rejections.

**The rejection of claims 23-31 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.**

The invention at issue are polynucleotides corresponding to genes that are expressed in cardiovascular, gastrointestinal, and reproductive tissues. The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptides coded for by the polynucleotides actually function.

Applicants submit with this response the Declaration of Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:1 and SEQ ID NO:2-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, infections, and vascular disorders for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

The Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function, or the biological function of the polypeptide it encodes. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise biological function.

## **I. The applicable legal standard**

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

An invention is “useful” under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) (“to violate Section 101 the claimed device must be totally incapable of achieving a useful result”); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention “is incapable of serving any beneficial end”).

*Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: “[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility.” *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a “nebulous expression” such as “biological activity” or “biological properties” that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be “substantial.” *Brenner*, 383 U.S. at 534. A “substantial” utility is a practical, “real-world” utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a “well-established” utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is no “well-established” utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office

bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a “substantial likelihood” of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

**II. Uses of the claimed polynucleotides for diagnosis of conditions and disorders characterized by expression of BMDSP, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph**

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are “well-established” uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application’s specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

**A. The use of BMDSP for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer “specific benefits” to the public**

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

The instant application is the National Stage of International Application No. PCT/US99/22908, filed October 1, 1999, which claims the benefit under 35 U.S.C. § 119(e) of provisional application U.S. Ser. No. 60/155,264, filed October 2, 1998 (hereinafter the Tang ‘264 application).



In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Tang '264 application on October 2, 1998 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, *e.g.*, ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration at, *e.g.*, ¶¶ 12 and 15).<sup>1</sup>

In connection with his explanations, Dr. Bedilion states that the "Tang '264 specification would have led a person skilled in the art on October 2, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, infections, and vascular disorders [a] to conclude that a cDNA microarray that contained the SEQ ID NO:1 and SEQ ID NO:2-encoding polynucleotides would be a highly useful tool, and [b] to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1 and SEQ ID NO:2-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on October 2, 1998] that a cDNA microarray that contained the SEQ ID NO:1 and SEQ ID NO:2-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, infections, and vascular disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-October 2, 1998 publications showing the state of the art on October 2, 1998 (Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his

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<sup>1</sup>Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Tang '264 specification, that the claimed polynucleotides would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

Declaration include almost three pages of text and six subparts (a)-(f), he specifically states that his explanations are not “all-inclusive.” *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on October 2, 1998 (and for several years prior to October 2, 1998) “without any doubt” appreciated that the toxicity (or lack of toxicity) of any proposed drug was “one of the most important criteria to be evaluated in connection with the development of the drug” and how the teachings of the Tang ‘264 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Tang ‘264 application at the time it was filed “would have wanted their cDNA microarray to have a [SEQ ID NO:1 or SEQ ID NO:2-encoding polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to October 2, 1998” (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Tang ‘264 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on pages 34 and Example VII on pages 40-41 of the Tang ‘264 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon v. Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the



invention works is irrelevant to utility); MPEP § 2107 (“Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)” (emphasis added)).

Though Applicants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating cancer, immune disorders, infections, and vascular disorders. Because the patent application states explicitly that the claimed polynucleotides are known to be expressed both in normal cells as well as cancerous and immortalized cells (see the Tang ‘264 application at pages 12-13), and expresses a protein that is a member of a class (family name) known to be associated with diseases such as cancer, immune disorders, infections, and vascular disorders, there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential cancer, immune disorders, infections, and vascular disorders drug candidate or potential toxin with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(f)).

The Bedilion Declaration shows that a number of pre-October 2, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Tang ‘264 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown ‘522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

The Brown ‘522 patent further teaches that the “[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention” can be used in “numerous” genetic applications, including “monitoring of gene expression” applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown ‘522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58; and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Tang '264 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.

\* \* \*

Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.

\* \* \*

Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis in original)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, Xenobiotica 29:655-691 (July 1999)).

In another article, Lashkari et al. state explicitly that sequences that are merely “predicted” to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proc. Nat. Acad. Sci. 94:8945-8947 (Aug. 1997) (emphasis added).

**B. The use of polynucleotides coding for polypeptides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now “well-established”**

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rocket et al., page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. “Arrays are at their most powerful when they contain the entire genome of the species they are being used to study.” John C. Rockett and David J. Dix, Application of DNA arrays to toxicology, Environ. Health Perspec.107:681-685 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.
- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte’s genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.
- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the “well-established” utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner’s rejections should be overturned regardless of their merit.

**C. The similarity of the SEQ ID NO:2 polypeptide encoded by the claimed invention to another polypeptide demonstrates utility**

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility of the claimed polynucleotide having the sequence of SEQ ID NO:4 can be imputed based on the relationship between the polypeptide it encodes, BMDSP-2, and another polypeptide of utility, MSE55. The two polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art would recognize more than a reasonable probability that the polypeptide encoded for by the claimed invention has utility similar to MSE55. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed, and readily apparent from the patent application, that the polypeptide encoded for by the claimed polynucleotide having the sequence of SEQ ID NO:4 shares more than 60% sequence identity over 42 amino acid residues with MSE55 (also referred to as Borg5), which is now known to be a member of the Borg family of proteins (See specification, for example, at page 14 and Figure 3). This is more than enough homology to demonstrate a reasonable probability that the utility of MSE55 can be imputed to the claimed invention (through the polypeptide it encodes). It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. (Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the polypeptide encoded for by the claimed polynucleotide is related to MSE55 is, accordingly, very high.

A recent BLAST analysis (Exhibit A) shows that SEQ ID NO:2 is 100% identical to human Borg2 (g5731207), another member of the Borg family related to MSE55. Members of the Borg family, including MSE55 and Borg2, serve as effectors for Rho GTPases, including TC10 and Cdc42, which regulate cytoskeletal remodeling, cell polarity, cytokinesis, and



vesicular transport. Members of the Borg family also serve as effectors for septin GTPases, which regulate cytokinesis, vesicular transport and cell polarity (Joberty et al. (1999) Mol. Cell. Biol. 19:6585-6597; and Joberty et al. (2001) Nat. Cell Biol. 3:861-866). Rho and septin GTPases have been implicated in cancer and neurological disorders (Boettner and Aelst (2002) Gene 286:155-174; Joberty et al. (2001), *supra*). This corroborates the statement on page 35 of the Specification that the SEQ ID NO:2 polypeptide and the polynucleotides encoding it may be useful in the diagnosis and treatment of cancer.

The Examiner must accept the Applicants' demonstration that the homology between the polypeptide encoded for by the SEQ ID NO:4 polynucleotide and MSE55 demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

**D. The fact that the SEQ ID NO:3 polynucleotide encodes a protein in the immunoglobulin family also demonstrates utility**

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, it is undisputed that the polynucleotide having the sequence of SEQ ID NO:3 encodes for the protein having the sequence shown as SEQ ID NO:1 in the patent application and referred to as BMDSP-1 in that application. Applicants have demonstrated that BMDSP-1 is a member of the immunoglobulin family, and that the immunoglobulin family of proteins includes immunoglobulins involved in the immune response (See specification, for example, at pp. 2 and 13). A recent BLAST analysis (Exhibit B) shows that the SEQ ID NO:1 polypeptide is 92% identical to the anti-rabies SOJA immunoglobulin kappa light chain (g27728685), thus corroborating a role for the SEQ ID NO:1 polypeptide and polynucleotides encoding it in the diagnosis and treatment of immune disorders and infections.

The Patent Examiner does not dispute that if a polynucleotide encodes for a protein that has a substantial, specific and credible utility, then it follows that the polynucleotide also has a substantial, specific and credible utility.

The Examiner must accept the applicant's demonstration that the polypeptide encoded by the claimed invention is a member of the immunoglobulin family and that utility is proven by a



reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the immunoglobulin family, let alone a substantial number of those members, is not useful. In such circumstances, the only reasonable inference is that the polypeptide encoded by the claimed invention must be, like the other members of the immunoglobulin family, useful.

**E. Objective evidence corroborates the utilities of the claimed invention**

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a “real-world” utility exists. “Real-world” evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants’ assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequences and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte’s customers and the scientific community have acknowledged that Incyte’s databases have proven to be valuable in, for example, the identification and development of drug candidates. Page et al., in discussing the identification and assignment of candidate drug targets, state that “rapid identification and assignment of candidate targets and markers represents a huge challenge ... [t]he process of annotation is similarly aided by the quantity and richness of the

sequence specific databases that are currently available, both in the public domain and in the private sector (e.g. those supplied by Incyte Pharmaceuticals)” Page, M.J. et al., “Proteomics: a major new technology for the drug discovery process,” *Drug Discov. Today* 4:55-62 (1999), see page 58, col. 2). As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte’s invention of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

### **III. The Patent Examiner’s rejections are without merit**

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not “specific, substantial, and credible” utilities. (Office Action at pages 3-6). The Examiner is incorrect both as a matter of law and as a matter of fact.

#### **A. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility**

The Patent Examiner’s primary rejection of the claimed invention is based on the ground that, without information as to the precise “biological role” of the claimed invention, the claimed invention’s utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug’s efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an “identifiable benefit” in presently available form. *Juicy Whip*

*Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called “throwaway” utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

[T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

**B. Because the uses of the claimed polynucleotides encoding BMDSP in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility**

The PTO rejected the claims at issue on the ground that the use of an invention as a tool for research is not a “substantial” use. Because the PTO’s rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section § 2107.01 of the Manual of Patent

Examining Procedure, 8<sup>th</sup> Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact “useful” in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The Patent Office’s actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO’s Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not “substantial” utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 (“What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.”). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a “substantial utility.” These include uses such as diagnostic assays (e.g., pages 34-40),

chromosomal markers (e.g., page 39), ligand screening assays (e.g., page 39), and drug screening (pages 39-40).

**IV. By requiring the patent applicant to assert a particular or unique utility, the Patent Examination Utility Guidelines and Training Materials applied by the Patent Examiner misstate the law**

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website [www.uspto.gov](http://www.uspto.gov), March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: “specific” utilities which meet the statutory requirements, and “general” utilities which do not. The Training Materials define a “specific utility” as follows:

A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as “gene probe” or “chromosome marker” would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between “specific” and “general” utilities by assessing whether the asserted utility is sufficiently “particular,” *i.e.*, unique (Training Materials at page 52) as compared to the “broad class of invention.” (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) (“With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.”)).

Such “unique” or “particular” utilities never have been required by the law. To meet the utility requirement, the invention need only be “practically useful,” *Natta*, 480 F.2d 1 at 1397, and confer a “specific benefit” on the public. *Brenner*, 383 U.S. at 534. Thus, incredible “throw-

away” utilities, such as trying to “patent a transgenic mouse by saying it makes great snake food,” do not meet this standard. Karen Hall, Genomic Warfare, *The American Lawyer* 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where “specific utility” is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be “definite,” not particular. *Montedison*, 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not “particular” or “unique” to the specific invention. Where courts have found utility to be too “general,” it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had “useful biological activity” was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a “particular” type of cancer was determined to satisfy the specificity requirement). “Particularity” is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison*, 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of “general” utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. See *supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.



**V. To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.**

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons.

**(9) CONCLUSION**

Applicants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of “lack of specificity,” as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, “like a nose of wax,”<sup>2</sup> to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

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<sup>2</sup>“The concept of patentable subject matter under §101 is not ‘like a nose of wax which may be turned and twisted in any direction \* \* \*.’ *White v. Dunbar*, 119 U.S. 47, 51.” (*Parker v. Flook*, 198 USPQ 193 (US SupCt 1978))

**Written description rejection under 35 U.S.C. § 112, first paragraph**

Claim 30 has been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

. . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (footnotes omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:3 and SEQ ID NO:4 are specifically disclosed in the application (see, for example, page 3, lines 33-34). Variants of SEQ ID NO:3 and SEQ ID NO:4 are described, for example, at page 4, lines 1-3. Incyte clones in which the nucleic acids encoding the human bone-marrow derived serum proteins (BMDSP) were first identified and libraries from which those clones were isolated are described, for example, at pages 13-14. Chemical and structural features of SEQ ID NO:1 and SEQ ID NO:2 are described, for example, at pages 13-14. Given SEQ ID NO:3 and SEQ ID NO:4, one of ordinary skill in the art would recognize a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical

to a polynucleotide sequence of SEQ ID NO:3 or SEQ ID NO:4. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

The Specification at page 5, lines 32-34, defines "BMDSP" as "the amino acid sequences of substantially purified BMDSP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or recombinant." Hence, by referring to polynucleotides encoding BMDSP, the Applicants clearly contemplated polynucleotides encoding SEQ ID NO:1 or SEQ ID NO:2 as well as naturally occurring variants thereof.

Additionally, the term "naturally occurring" is a well-known term in the art which Applicants intended to be used in such context. As such, no further definition of the term is necessary (MPEP 2163 IIA3(a)):

What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

One of ordinary skill in the art would recognize that "a naturally occurring polynucleotide sequence" as recited in claim 30 is one which occurs in nature. Through the process of natural selection, nature will have determined the appropriate polynucleotide sequences. Given the information provided by SEQ ID NO:3 (the polynucleotide sequence encoding BMDSP-1) and SEQ ID NO:4 (the polynucleotide sequence encoding BMDSP-2) one of skill in the art would be able to routinely obtain a polynucleotide at least 90% identical to the polynucleotide sequence of SEQ ID NO:3 or SEQ ID NO:4. For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application (See Specification, e.g., at p. 23, lines 1-12; p. 35, lines 6-25; and Example VI at p. 45).

The Office Action has further asserted that the claims are not supported by an adequate written description because "[t]he specification lacks description or exemplification of any

activity for the polynucleotides and the encoding polypeptides" (Office Action at page 6).

Applicants respectfully point out that the claims are directed to polynucleotides, not polypeptides, and it is the functionality of the claimed polynucleotides, not the polypeptides encoded by them, that is relevant. Members of the claimed genus of variants may include, for example, mutant alleles associated with diseases, or single nucleotide polymorphisms (SNPs). Members of the claimed genus of variants may encode defective polypeptides, including variants that may be associated with disease states, such as the diseases listed on page 35, line 26 through page 36, line 32, of the specification.

Such a position is believed to present a misapplication of the law.

**1. The present claims specifically define the claimed genus through the recitation of chemical structure**

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than functional characteristics. For example, the "variant language" of independent claim 30 recites chemical structure to define the claimed genus:

30. An isolated polynucleotide selected from the group consisting of:...
- b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:4...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1-4. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural

characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

## 2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that  $\geq 40\%$  identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to bone marrow-derived serum proteins related to the amino acid sequences of SEQ ID NO:1 or SEQ ID NO:2. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as bone marrow-derived serum proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1 or SEQ ID NO:2. The "variant language" of the present claims recites, for example, polynucleotides encoding "a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1" or "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence SEQ ID NO:2" (note that SEQ ID NO:1 and SEQ ID NO:2 have 234 and 254 amino acid residues, respectively). This variation is far less than that of all potential bone marrow-derived serum proteins related to SEQ ID NO:1 or SEQ ID NO:2, i.e., those bone marrow-derived serum proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1 or SEQ ID NO:2.



**3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications**

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of July 7, 1999. Much has happened in the development of recombinant DNA technology in the 20 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1-4, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

**4. Summary**

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structures of SEQ ID NO:1-4. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state

of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

### **Rejections under 35 U.S.C. § 112, second paragraph**

Claims 23-31 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite (Office Action, page 8). In particular, the Office Action alleges that claims 23, 24, and 28, as well as their dependent claims, are indefinite because of their dependence from non-elected claims. Although not conceding to the propriety of the rejection, in order to expedite prosecution, claims 23 and 28 have been amended such that they no longer depend on non-elected claims. Claim 24 has been canceled; therefore, the rejection with respect to this claim is moot. Therefore, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

### **Rejections under 35 U.S.C. § 102(a)**

Claims 23 and 31 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Alberts et al. (1998) J. Biol. Chem. 273: 8615-8622 (Office Action, page 8). Applicants respectfully traverse the rejection.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102(a), "the reference must teach every aspect of the claimed invention either explicitly or implicitly." The rejection under 35 U.S.C. § 102(a) is improper because the sequences of the MSE55-related protein and the polynucleotide encoding it ( GenBank Accession No. AF094521) are not disclosed in the reference of Alberts et al. The authors merely refer to some unpublished work on the MSE55-related protein and the use of the MSE55-related protein as a control to "confirm the specificity" of interactions with Cdc42 of various proteins identified in a yeast two-hybrid screen (See Albert et al. at p. 8618, col. 1). Applicants note that the priority date for the sequence of SEQ ID NO:4 of the instant application is October 2, 1998. The GenBank entry for the MSE55-related protein (AF094521) was first publically available on November 5, 1998 (Exhibit C), and therefore does not constitute prior art under 35 U.S.C. § 102(a).

Since the reference of Alberts et al. does not disclose 60 contiguous nucleotides that are identical to SEQ ID NO:4 as recited in claim 31, nor a polynucleotide encoding an immunogenic fragment of at least 20 contiguous amino acid residues of an amino acid sequence of SEQ ID NO:2 as recited in claim 23, the limitations of the claims are not taught by the reference. For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 102(a) is respectfully requested.

**CONCLUSION**

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

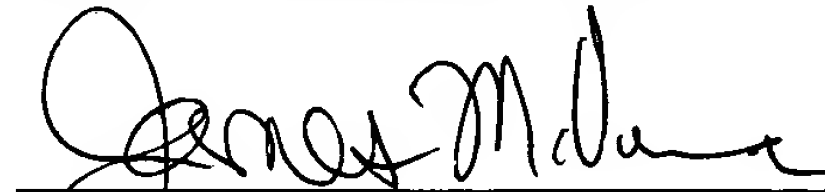
If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

Respectfully submitted,

INCYTE CORPORATION

Date: 8 December 2003

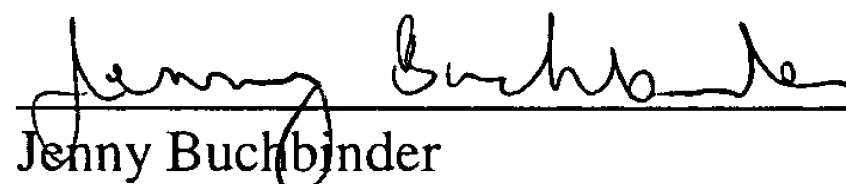


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Enclosures:

1. Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, Xenobiotica 29:655-691 (1999)
2. Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proc. Nat. Acad. Sci. 94:8945-8947 (1997).

3. Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999);
4. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000).
5. John C. Rockett and David J. Dix, Application of DNA arrays to toxicology, 107 Environ. Health Perspec. 107:681-685 (1999).
6. Email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding,
7. Brenner et al., Proc. Natl. Acad. Sci. 95:6073-6078 (1998).
8. Page, M.J. et al., Proteomics: a major new technology for the drug discovery process, Drug Discov. Today 4:55-62 (1999).
9. Joberty et al., Mol. Cell. Biol. 19:6585-6597 (1999).
10. Joberty et al., Nat. Cell Biol. 3:861-866 (2001).
11. Boettner and Aelst, Gene 286:155-174 (2002).
12. Exhibit A
13. Exhibit B
14. Exhibit C